to at least a portion of the mammalian skin affected by psoriasis and exposing the agent to electromagnetic radiation of at least the first wavelength. The agent absorbs the first wavelength of electromagnetic radiation. The electromagnetic radiation source is at least one light emitting diode (LED).

In contrast, while Doiron discloses a system that includes an array of LEDs for phototherapy, Doiron does not teach or suggest a system that includes selecting at least one of a photoactive and a photosensitizing agent with an electromagnetic radiation absorption characteristic enabling the agent to absorb at least a first wavelength of electromagnetic radiation from an electromagnetic radiation source, applying the agent to at least a portion of the mammalian skin affected by psoriasis and exposing the agent to electromagnetic radiation of at least the first wavelength.

The Examiner asserts that Doiron's Background section teaches a method of treating psoriasis with the aid of a photoactive agent applied to the skin and irradiating the skin with optical energy from an LED array that was known in the art, pointing to Jori's *Porphyrins in Tumor Therapy* (a readable copy of which is attached and is also being provided to the Examiner by email). Applicant respectfully disagrees. The Examiner has apparently misread Doiron, especially the section at col. 3, lines 36-52 that alludes to Jori. Specifically, Doiron fails to teach or suggest a photoactive and a photosensitizing agent used to treat psoriasis: it merely discloses an LED array. Similarly, Jori does not teach or suggest using an LED array to treat psoriasis. Rather, Jori's teaching is limited to using an LED array to treat tumors and the use of hematoporphyrin, which is a drug that that is absorbed by tumor cells and when exposed to light, becomes active and kills the cancer cells. That is not the claimed invention.

Applicant's claimed invention clearly requires all of the following: 1.) selecting at least one of a photoactive and a photosensitizing agent, 2.) applying the agent to at least a portion of the mammalian skin affected by psoriasis, 3) exposing the agent to electromagnetic radiation and 4.) an

electromagnetic radiation source that is at least one LED. Both Doiron and Jori are devoid of any teaching or suggestion that would have motivated one skilled in the art to modify the reference or to combine reference teachings to arrive at the claimed invention. To anticipate a claim, the reference must teach every element of the claim. Doiron fails to do this and Jori does not cure this defect. Accordingly, the invention claimed is patentable over the prior art, and claim 7 should be allowed. This logic also disposes of the rejection of claim 9, which depends directly from claim 7.

The Examiner also rejected claims 7-9 under 35 USC 103(a) as being unpatentable over Hartman U.S. Patent No. 6,413,268 in view of Doiron and claim 10 under 35 USC 103(a) as being unpatentable over Hartman in view of Doiron and Tankovich U.S. Patent No. 5,817,089. Applicant respectfully traverses these rejections. These rejections are untenable because the combination constructed by the Examiner is not the claimed invention. Thus, the invention could not have been obvious, even in hindsight.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not be based on an applicant's disclosure. MPEP 2143.

The Examiner asserts that Hartman, at col. 1, lines 22-24, allegedly teaches that the use of photoactive agents during phototherapy treatment of psoriasis is well known in the art. Applicant respectfully disagrees. In the cited section, Hartman states that "[t]reatment with UVA radiation is called photochemical therapy and involves the use of a photosensitizing agent, psoralen, and the administration of UVA radiation" (PUVA). The reasons why PUVA treatment works remains

unclear, though there may be effects on cell turnover and the skin's immune response. That is not the claimed invention.

The Examiner then admits that Hartman does not disclose the clamed LEDs and then asserts that it would have been obvious to modify Hartman in view of Doiron to use an LED to provide the treatment energy. Applicant respectfully disagrees. Doiron and Hartman do not suggest at all - or show a reasonable expectation of success - a system that includes selecting at least one of a photoactive and a photosensitizing agent with an electromagnetic radiation absorption characteristic enabling the agent to absorb at least a first wavelength of electromagnetic radiation from an electromagnetic radiation source, applying the agent to at least a portion of the mammalian skin affected by psoriasis and exposing the agent to electromagnetic radiation of at least the first wavelength. Combining Doiron and Hartman requires impermissible hindsight.

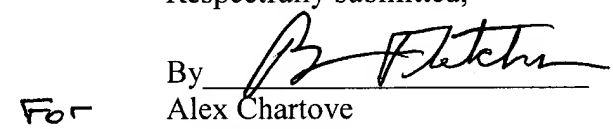
Even if the resulting combination suggested by the Examiner included all the limitations of claim 7, the cited references provide no evidence of a motivation to combine their disclosures so as to arrive at the claimed invention. The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination. Doiron is directed to a light delivery device that includes an array of LEDs. Hartman is directed to a phototherapy apparatus with a UVB arc lamp and an output port for delivery of UVB radiation within a predetermined range. Doiron and Hartman neither use nor suggest all the features in applicant's claimed invention. The Examiner has pointed to no disclosure in Doiron, the alleged evidence of such a motivation, which would have motivated a person of ordinary skill in the art to look to Hartman for combination with Doiron to arrive at the claimed invention. Applicant's invention may be a straightforward and elegant solution to the problem it addresses, but the cited prior art is devoid of a suggestion to make it. Accordingly, the invention claimed is patentable over the prior art, and claim 7 should be allowed. This logic also disposes of the rejections of claims 8-10, which depend directly from claim 7.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 595982000211.

Dated: September 25, 2006

Respectfully submitted,

By  #51,683

For Alex Chartove
Registration No.: 31,942
MORRISON & FOERSTER LLP
1650 Tysons Blvd, Suite 300
McLean, Virginia 22102
(703) 760-7744

Attachment

A MULTI-LED SOURCE FOR PHOTORADIATION THERAPY

Giulio Jori, Riccardo Fratesi[+], and M. Scalvini[o]

Istituto di Biologia Animale, Università di Padova
Italy

[+] Istituto di Fisica Superiore dell'Università, Istituto di Elettronica Quantistica, CNR, Firenze, Italy

[o] MASPEC - CNR, Parma, Italy

INTRODUCTION

Light sources emitting at the long wavelength wing of the absorption spectrum of Hematoporphyrin (Hp), between 610 and 640 nm, are currently used in photoradiation therapy (PRT) in order to maximize penetration of light into the tumor mass. Optical output powers of several watts are necessary to ensure the suitable irradiance (30÷100 mW/cm^2) at the tumor surface. Filtered high-power Xenon or halogen lamps, and ion-laser-pumped dye lasers tuned at $\lambda_p \simeq 630$ nm are the most common sources used so far. The overall electrical-to-optical conversion efficiency of these sources is quite small, typically 0.05% (0.2 for halogen lamps). Flash-lamp-pumped dye lasers are now commercially available at average output power of 10÷20 W; the efficiency is ∿ 0.8% in the red [1]. Their use for photodynamic therapy is under investigation [2]. Gold vapor lasers emitting 1÷6 W at 628 nm with 0.2% efficiency represent another interesting new source for PRT of tumors [3].

A different class of light sources that could find application in the PRT of tumors is represented by Light Emitting Diodes (LEDs). These miniaturized solid-state lamps have been used almost exclusively as very low power indicators and displays untill recently; now the application in several growing fields (such as optical communications) has led to the development of high-efficiency, high-intensity LEDs. Red light emitting diodes are today commercially available at output powers of several milliwatts with an efficiency of ∿ 5%, and at low cost. As the emitted wavelengths range from

) to 680 nm a suitably shaped multi-LED system cou
cessary power density for the PRT of superficial t
lopment of tightly-packed arrays of incoherent or
fficiency LEDs may lead to more compact sources fo
rticular, to efficient optical fiber systems for e
nts.

In this paper the possibility of utilizing a mu
light source to promote porphyrin-sensitized phot
es tested by following the Hp-sensitized photooxid
dnoacid L-tryptophan (Trp) either free or bound wi
bumin (HSA), as well as the Hp-sensitized photokil
:lls. Both these systems have been previously inve
g conventional light sources [4,5].

ATERIALS AND METHODS

The H-500 Hi-super bright red LED (GaAlAs) mad
.ectric Co, Ltd (Japan) has been chosen for the ex
nal values of output intensity, peak wavelength an
ldth at i_F = 20 mA forward current (f.c.) and room
= 500 mcd; λ_0 = 660 nm; $\Delta\lambda$ = 40 nm, respectively.
ameters are strongly temperature dependent. A dec
rating temperature produces a blue-shift of the pe
nd a narrowing of the output spectrum; the total l
ncreases by several orders of magnitude when the d

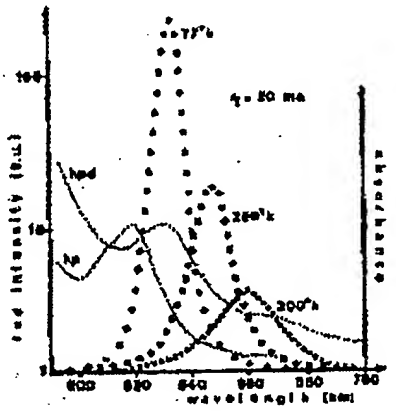


Fig. 1.

at 77°K. Fig. 1 shows the emission spectra (at 20 mA f.c.) of the H-500 LED at several temperatures, together with the absorption spectra of Hp and Hp derivative (HpD). As it can be seen, at room temperature the absorption by Hp is expected to be low due to the 30 nm shift between LED emission and Hp absorption maxima[4]. By reducing the LED temperature, the emission maximum can be brought into coincidence with the 630 nm peak of HpD: the narrower spectrum and the much higher intensity should now greatly enhance the efficiency of the LED to excite HpD molecules.

In the experiment the H-500 LED has been operated at room temperature and at 50 mA f.c.: output powers greater than 3 mW has been measured in these conditions. The LED collimating capsule provides a half-intensity full-divergence of 45°, i.e. half power of the LED can be collected on 1 cm^2 area target placed at 13.5 mm from the capsule. Thirtythree LEDs have been inserted into closely-packed, radially oriented holes in a metallic hemisphere with 15 mm inner diameter. The light intensity distribution over the central 1 cm^2 spot in the equatorial plane was sufficiently uniform with a power density of ~ 27 mW/cm^2 (at 50 mA f.c.).

RESULTS AND DISCUSSION

Hematoporphyrin-sensitized photooxidation of tryptophan and the tryptophyl residue of human serum albumin

When 0.7 ml of a 0.1 mM Trp solution in 0.05 M phosphate buffer at pH = 7.4 was irradiated in the presence of 100 μM Hp at ca. 20°C, the aminoacid underwent photooxidative modification according to first-order kinetics (Fig. 2.a,b). Such a behaviour is typical of porphyrin-promoted photodynamic processes[6]. The rate constant of the photoprocess was 1.3 $10^{-4}s^{-1}$, i.e. one order of magnitude lower than that observed for the same system exposed to a He-Ne laser emitting ca. 25 mW/cm^2 at 632.8 nm[7]. The rate constant almost doubled (Fig. 2.b) when HSA-bound Hp was used as a photosensitizer for the modification of the unique Trp residue present in HSA. Under our experimental conditions, Hp yields a 1:1 ground state complex with HSA, the porphyrin binding site being at 1.7 nm from the indole side chain of the Trp residue[8]. The enhancement of the rate constant for photoprocesses promoted by protein-bound porphyrins has been previously observed[9] and ascribed to a greater triplet quantum yield for bound Hp as compared with free Hp and/or a shift in the overall photooxidation mechanism from a type II ($^1O_2$-involving) pathway to a type I (radical-involving) pathway.

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[4] At the time of the experiment the Hewlett-Packard LED HP 3750 emitting 160 mcd at 635 nm was not available. Its better matching of Hp absorption should compensate for the lower emission power.

Fig. 3.

Arrays

Straightforward hybrid-circuit fabrication techniques should mit the assembly of single LED chips into tightly-packed arrays able of producing the irradiance needed for PRT, as already posed by Epstein et al. [11]. Integrated optical systems could n provide the suitable radiation pattern or efficient coupling optical fiber delivery systems. Fig. 3 shows a picture of a 2 array of four IR LEDs already available commercially.

de Lasers and Diode Laser Arrays

A number of single-emitter conventional semiconductor diode ers emit output powers in excess of 50 mW cw from a single facet the near IR [12]. For red diode lasers begin to be produced at er power (10÷20 mW). Future development of high power diode ers at $\lambda \approx 630$ nm should permit very compact and efficient multi- ement sources for PRT.

Recently, cw operation of multiemitter (40) phase-locked arrays IR diode lasers has also been demonstrated at output power levels great as 2.5 W [12]. Because the emission is coherent, the laser ht can be focused into a single diffraction-limited spot. When ilar powers will be available in the useful porphyrin absorption ge, important progresses will be registered in the phototechnol- of tumor therapy.

CONCLUSIONS

In this paper evidence has been presented that red light emitting diodes (LEDs) can be used to kill porphyrin-sensitized tumor cells. Multi-LED systems can provide the power density needed for therapy of superficial tumors. Operation of multi-LED (M-500) arrays at 77°K is expected to produce much higher power densities and to allow direct LED coupling to optical fibers for the treatment of internal tumors with large bore endoscopes. The application to PDT of future developments of incoherent LED-arrays, diode lasers, and diode laser arrays has also been discussed.

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